

## REMARKS

The Final Office Action of September 9, 2004, has been received and reviewed. Claims 4 through 6 and 21 through 29 are currently pending, and all stand rejected. Applicants are amending claims 4, 6, 21, and 27 as set forth herein. All amendments and cancellations are made without prejudice or disclaimer. No new matter has been added. Reconsideration is respectfully requested.

### A. Substance of the Interview

Applicants would like to thank the Examiner for the courtesy extended to applicants' representatives during the Interview of January 25, 2005. As discussed at the interview, applicants would file a request for continued examination and submit to the Office various references presented in the parallel opposition and litigation proceedings in Europe. Applicants would also consider clarifying the claim language as set forth herein. The results of comparative Example 1 and Example 2 were specifically discussed, especially with respect to the results of the aging process and the resulting reduced impurity in the crystals described in Example 2. (See, also, Interview Summary of January 25, 2005). Applicants believe this statement together with the draft presented at the Examiner Interview adequately summarizes the interview. Further, this Amendment is intended to set forth applicants' complete written statement of the reasons presented at the Interview as warranting favorable action. (*Cf.*, 37 C.F.R. § 1.133(b)).

### B. 35 USC § 112, 2<sup>nd</sup> paragraph

Claims 21, 24, 25, and 28 stand rejected under the second paragraph of 35 USC § 112 for lack of antecedent basis for "Org OM38 as an impurity". As discussed at the interview, applicants have amended base claim 4 to clarify that the process is one for "reducing the rate of formation of (7 $\alpha$ , 17 $\alpha$ ) -17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-oneone impurity in" crystals of tibolone. Specific basis for this amendment can be found at page 3, lines 9 through 11 in conjunction with page 2, lines 3 and 4 of the application as-filed. In view of the amendment, applicants request that the rejection be withdrawn.

**C. 35 USC § 103**

Claims 4 through 6 and 21-29 stand rejected as being obvious over Sas et al. and van Vliet et al. Applicants respectfully traverse the rejection.

As discussed at the interview, neither Sas et al. nor van Vliet et al. teach or suggest aging at all, let alone “aging crystals of [tibolone] in the presence of water for a period of time of at least 24 hours” as required by each of the pending claims. Roberts et al. does not overcome this deficiency.

Specifically, Sas et al. (see, Example 4) discloses a process for preparing crystals of tibolone wherein a solution of tibolone in ethanol and some pyridine was poured into water and some pyridine, the resulting crystals then were filtered off, washed with water and some pyridine, and dried under vacuum. A process very similar to this process is described in Comparative Example 1 of the subject application, *i.e.*, a solution of tibolone in ethanol, some pyridine, and water was poured into water and some pyridine, the resulting crystals (‘suspension’) then were filtered off, washed with water and some pyridine, and dried under vacuum.

Example 2 of the subject application describes a process in accordance with the invention in which a solution of tibolone in ethanol, some pyridine, and water was poured into water and some pyridine, the resulting crystals (“suspension”) then were filtered off, washed with water and some pyridine, then were allowed to age for 3-6 days at room temperature - in accordance with claim 4-, and thereafter dried under vacuum. As further discussed at the interview, such aging in a non-solvent for tibolone unexpectedly results in tibolone having a low Org OM38 content as well as having greater stability, especially with respect to Org OM38 formation. These results are all the more surprising, because tibolone does not dissolve in water (*i.e.*, since water is a non-solvent for tibolone) and one of ordinary skill in the art would not have considered contacting crystals of tibolone with water for any prolonged period of time to begin with (wet crystals are typically dried immediately in order to prevent decomposition), let alone aging the crystals for a period of time of at least 24 hours.

As requested by the Examiner, a side-by-side comparison of Comparative Example 1 and Example 2 is given in the following Table:

Comparative Example 1	Example 2
A solution of A* in a mixture of pyridine and water, was	A solution of A* in a mixture of pyridine and water, was
mixed with a solution of oxalic acid in water,	mixed with a solution of oxalic acid in water,
mixture was stirred,	mixture was stirred,
solution was poured out in a mixture of pyridine and water,	Solution was poured out in a mixture of pyridine and water,
resulting suspension ('crystals') was filtered,	Resulting suspension ('crystals') was filtered,
crystals were washed with a mixture of water and pyridine, and	crystals were washed with a mixture of water and pyridine,
	(wet) crystals were allowed to age for 3-6 days at room temperature, and
crystals were dried under vacuum.	crystals were dried under vacuum.
Analysis results	Analysis result
Tibolone containing 0.6% of Org OM38	Tibolone containing 0.1% of Org OM38
0.4% increase of Org OM38 after 1 month	0.1% increase of Org OM38 after 1 week

A\* is (7 $\alpha$ , 17 $\alpha$ ) -3,3-dimethoxy-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one

As discussed at the interview, although there are minor differences between the reaction conditions of Comparative Example 1 and Example 2 of the as-filed Specification (*e.g.*, use, in Comparative Example 1, of 750 grams of oxalic acid to remove the methoxy moieties rather than 375 grams as in Example 2, and stress testing at 45° C for 1 month in Comparative Example 1 versus 1 week in Example 2), one of skill in the art would conclude that the crystals of Example 2 aged for 3 to 6 days were purer (containing less than 0.1% Org OM38 in Example 2 versus

0.6% Org OM38 in Comparative Example 1) and more stable (displaying less than 0.1% increase of Org OM38 after 1 week in Example 2 versus 0.4% increase of Org OM38 after 1 month in Comparative Example 1).

In view of the foregoing, applicants respectfully submit that the obviousness rejection should be withdrawn.

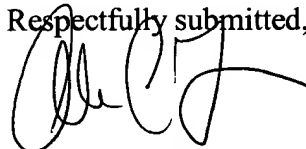
#### D. New References

As agreed at the interview, applicants submit herewith new materials relevant to the parallel European and UK proceedings. As discussed at the interview, Alexéev is believed to be the only reference submitted herewith that mentions "aging" in that it discloses the maturation or aging of BaSO<sub>4</sub> crystals. This "aging", however, is actually only "Ostwald ripening" of the crystals in a solvent for the compound, and not the claimed aging in a non-solvent (*i.e.*, water) for the compound. Ostwald ripening is a well-known process in which smaller crystals go into solution (and the larger crystals grow larger) and an overall increase in the size (and purity) of the particles is achieved. This process thus requires a solvent for the compound.

#### Conclusion

In view of the foregoing, the application should be in condition for allowance. If questions should remain after consideration of the foregoing, however, the Office is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



Allen C. Turner  
Registration No. 33,041  
Attorney for Applicants  
TRASKBRITT, P.C.  
P.O. Box 2550  
Salt Lake City, Utah 84110-2550  
Telephone: 801-532-1922

Date: February 9, 2005